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Pneumococcal Polysaccharide Vaccination in Pediatric Inflammatory Bowel Disease

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Abstract

According to current recommendations, in addition to 13-valent pneumococcal conjugate vaccine (PCV13) series, all children with inflammatory bowel disease (IBD) aged ≥2 years, with planned or current immunosuppression, should receive pneumococcal polysaccharide vaccine (PPSV23). The primary aim was to determine the PPSV23 immunization rates in our pediatric IBD patients. The secondary aim was to determine the incidence of invasive pneumococcal disease in these patients. The IBD database at Le Bonheur Children's Hospital was retrospectively reviewed to identify all cases diagnosed from 2003 to 2015. Out of 190 IBD patients, 106 on immunosuppressive drugs, whose immunization records could be obtained from the state database, were included in the study. Medical records were reviewed to determine infections seen in these patients from the time of diagnosis to date. IBD patients in our study ranged from age 2 to 18 years. Only 4 of 106 (3.7%) patients had received PPSV23 vaccine. Only 1 patient (0.9%) had probable pneumococcal disease and none with invasive pneumococcal disease. *Clostridium difficile* (11 patients) and *Cytomegalovirus* colitis (4 patients) were more commonly encountered. All our patients received the recommended PCV13 vaccine. The majority of our pediatric IBD patients did not receive PPSV23 vaccine. Fortunately, we did not see a high rate of invasive pneumococcal disease in our patients suggesting that they may be protected by the primary PCV13 vaccine series. Non-pneumococcal infections were more common in this population.

Keywords

pneumococcal infections, vaccines, inflammatory bowel disease, pediatrics, infection

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Introduction

Patients with inflammatory bowel disease (IBD) are at increased risk of infection, particularly those on high-level immunosuppression.[1] Prior studies have shown an increased risk of pneumococcal pneumonia in adults with IBD,[2,3] and immunization is recommended to prevent this infection.

Since the advent of the pneumococcal vaccine in 2000, there has been a significant decline in invasive pneumococcal disease (IPD), defined as culture-proven pneumonia, meningitis, or bacteremia.[4] The rate of IPD in healthy children aged 5 to 17 years decreased from 4.2 per 100 000 to 3.4 per 100 000 after introduction of 7-valent pneumococcal conjugate vaccine (PCV7), and further declined to 1.3 per 100 000 after introduction of 13-valent pneumococcal conjugate vaccine (PCV13) in 2010.[5,6] All children are currently recommended to receive 4 doses of PCV13 between 2 months and 15 months old. Additionally, for immunocompromised children who received the PCV7 vaccine series, an additional single dose of PCV13 is recommended to complete their pneumococcal vaccination series.[7]

The current recommendation from the Infectious Disease Society of America (IDSA) is to administer pneumococcal polysaccharide vaccine (PPSV23), in addition to routine childhood vaccines, to IBD patients with planned or current high-level immunosuppression, defined as prednisone >2 mg/kg or >20 mg/day, methotrexate

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Table 1. Gender Distribution of Crohn's Disease and Ulcerative Colitis.

	Crohn's Disease	Ulcerative Colitis
Total number	74	32
Male	52	16
Female	22	16

>0.4 mg/kg/week, azathioprine >3 mg/kg/day, 6-mercaptopurine >1.5 mg/kg/day, or biologics such as tumor necrosis factor (TNF) antagonists.[1] The incidence of IPD has not been established in pediatric IBD.

The primary aim of this study was to determine the PPSV23 immunization rates in our pediatric IBD patients on high-level immunosuppression. The secondary aim was to determine the incidence of pneumococcal disease in these patients.

Materials and Methods

This was a retrospective single institution study at Le Bonheur Children's Hospital in Memphis, Tennessee. We identified and reviewed the electronic medical records of all pediatric IBD patients from age 2 to 18 years diagnosed between 2003 and 2015 who were on high-level immunosuppression.[1]

Immunization records for these patients were obtained from the Tennessee state immunization database, as well as from the electronic medical record. For incomplete immunization records, we attempted to contact the primary care provider for updated records. Patients were excluded from the study if complete records could not be obtained. Patients were also excluded if they had comorbidities that were independent risk factors for pneumococcal infection, such as primary immunodeficiency states or any non-IBD conditions that require immunosuppressive drugs, such as nephrotic syndrome.

We reviewed both ambulatory gastroenterology clinic records and inpatient medical records of all study patients to identify the infections they had during the study period while on immunosuppressive therapy. Specifically, we identified all documented pneumococcal infection. We defined pneumococcal infection as invasive pneumococcal infections (bacteremia or meningitis) or suspected pneumococcal pneumonia, which was determined by the need for anti-pneumococcal antibiotic therapy.[4]

Ethical Approval and Informed Consent

The study was approved by the University of Tennessee Institutional Review Board (Approval No. 612011), which provided ethical approval for this study. The institutional review board provided a waiver of informed consent for collection and analysis of the retrospectively obtained and anonymized data.

Results

There were 190 pediatric IBD patients on high-level immunosuppression, 83 were excluded because of incomplete immunization records or out-of-state residence, and 1 was excluded for diagnosis of nephrotic syndrome as this independently increased his risk of IPD. There were 106 patients included in the study, of which 32 (30%) had ulcerative colitis and 74 (70%) had Crohn's disease (CD; Table 1). Age distribution included 6 (6%) from age 2 to 5 years, 31 (29%) from age 6 to 11 years, and 69 (65%) from age 12 to 18 years.

Of these patients, most (100/106, 94.3%) had completed the PCV7 series, and they all later received a single dose of PCV13 vaccine. Six patients were born during or after 2010 when PCV13 was introduced, and thus completed the full PCV13 vaccine series. Only 4 patients (3.7%) had received the PPSV23 vaccine of 106 patients who qualified per the IDSA guidelines for increased risk due to immunosuppression. Of these, 2 received the vaccine at our institution and 2 at their primary care provider's office. None of the patients included in the study had IPD. One patient had probable pneumococcal pneumonia, but this occurred prior to diagnosis of IBD and hence was prior to initiation of immunosuppressive medications. There were 48 occurrences of infections in our study population, which included *Salmonella* enteritis, group A streptococcal pharyngitis, *Clostridium difficile*, and various viral infections including adenovirus, influenza, herpes simplex virus, varicella, cytomegalovirus, and rotavirus. There were also patients with intraabdominal abscesses related to CD (Figure 1). The disease duration of our patients ranged from 2 to 12 years from time of diagnosis, with an average of 4.5 years.

Discussion

Chronic diseases and immunodeficiencies in pediatric patients increase their susceptibility to IPDs, but the evidence for that is lacking in pediatric IBD.[8] The increased risk of general infections in IBD patients is thought to be multifactorial. The altered innate immune response predisposes to increased susceptibility to infections.[9] Moreover, the mainstay therapy of IBD includes immunosuppressive agents, which further increase the risk of bacterial infections in patients with IBD.[10,11] Studies in adults with IBD have previously shown a significant increase in incidence of IPD in hospitalized patients with immune-mediated diseases such as CD and ulcerative colitis compared with other hospitalized patients,[12]

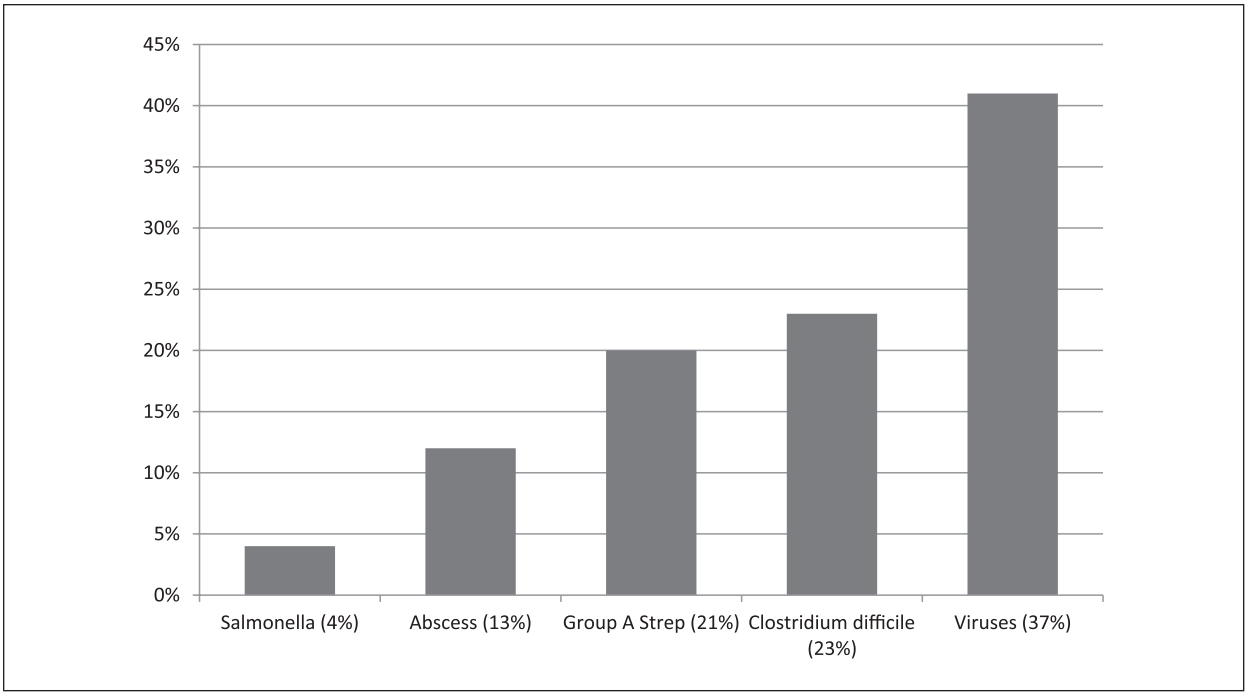

Figure 1. Infections in pediatric inflammatory bowel disease on high-level immunosuppression.

with an incidence rate ratio of 1.82.[3] This increase in risk is not well established in pediatric IBD patients. In our retrospective single-institution study, the majority of pediatric IBD patients on high-level immunosuppression did not receive the PPSV23 vaccine despite the current recommendations. Fortunately, this was not accompanied by a corresponding increase in the incidence of IPD. We propose that the reason for the low incidence of IPD in pediatric IBD patients might be due to presence of protective levels of anti-pneumococcal antibodies from the primary vaccination series. Further studies looking at the pre-immunization anti-pneumococcal antibody titers may be needed to better understand the rationale for this lower incidence of IPD. These studies may lead to developing a more targeted approach to vaccinating only a subset of children with IBD with PPSV23 or delaying it until a specific age.

A study in cystic fibrosis patients showed that the majority of cystic fibrosis patients had protective levels of anti-pneumococcal antibody prior to immunization with PPSV23.[13] Non-pneumococcal infections were more commonly seen in this population, such as *Pseudomonas aeruginosa, Staphylococcus aureus*, and *Haemophilus influenzae*.

The guidelines from IDSA recommend administration of PPSV23 vaccine to patients older than 2 years of age with chronic inflammatory illnesses on immunosuppressive therapy, with an additional dose 5 years later.[1] Previous studies in adult gastroenterology literature have demonstrated an increased risk of pneumonia in IBD patients as compared with the general population.[2,3,14] This risk has been attributed to immunosuppressive medication use in this population, including steroids, immunomodulators, and anti-TNF-α therapy.[9,15] The incidence of pneumococcal infections in pediatric IBD has not been established, and recommendations for this population come from adult literature.

In contrast with adult studies, none of the patients in our retrospective study had IPD. Our data suggest that pediatric IBD patients on immunosuppression may not be at an increased risk of invasive pneumococcal infection compared with the general population. This difference might be explained by waning immunity to the routine childhood PCV series in adults. A limitation of our study is that our population is limited to a single institution and includes a relatively small sample size. Subsequently, we would not presume to recommend that clinicians do not follow the recommended IDSA guidelines. However, future multicenter studies are needed to determine the true incidence of IPD in the pediatric IBD patient populations and evaluate the recommendation for PPSV23 in children with IBD on immunosuppressive therapy.

Due to the retrospective nature of our study, an additional limitation is that we were only able to access data from our institution, so did not include any visits to primary care physicians. Our study identified 48 occurrences of documented infection, but we only

included occurrences of infections that required hospitalization or gastroenterology clinic visits as these had available electronic medical records. While this allowed us to focus our study on documented infections and not rely on parental recall, it excluded minor infections that self-resolved or were managed by the pediatrician. While the focus of our study was IPD, it is important to acknowledge that noninvasive pneumococcal infections, such as otitis media, expose our IBD patients to antibiotics and can affect quality of life by causing additional school absences for our chronic disease population.

Conclusion

All our pediatric IBD patients received the recommended PCV13 vaccine; however, the majority of our patients did not receive PPSV23 vaccine. Fortunately, we did not see a high rate of IPD in our patients suggesting that they may be protected by the primary PCV13 vaccine. Non-pneumococcal infections were more common in our pediatric IBD population.

Author Contributions

Tsega Temtem, MD contributed to conception and design; drafted manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.
John Whitworth, MD contributed to conception and design; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.
Bindiya Bagga, MD contributed to conception and design; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of Conflicting Interests

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